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Heterocycles via Pd catalysed molecular queuing processes. Relay switches and the maximisation of molecular complexity

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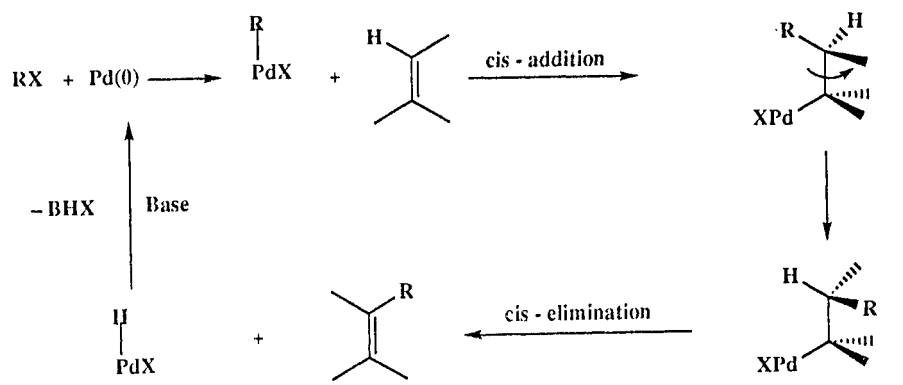
Abstract: Pd(0) catalysts facilitate the assembly of complex heterocycles and carbocycles containing 3 - 7 membered rings from a range of simple building blocks (allenes, carbon monoxide, alkenes, organometallic complexes of B, Zn, Sn etc.). These cascade processes display remarkable chemo-, regio- and stereo-selectivity and considerably extend the scope and utility of our previously developed cyclisation-anion capture cascades. The success of these processes is critically dependant on the relative rates of a range of potentially competing processes and the various substrates can be regarded as queuing for access to the catalytic metal centre. Certain compounds are identified as relay switches because they extend the relay phase of the cyclisation-anion capture cascade whilst allowing the Pd catalysed cascades to switch between inter- and intra-molecular processes.

Palladium salts and complexes are exceptionally versatile catalysts for the construction of carbon-carbon and carbon-heteroatom bonds.[1] Much recent attention has focused on the Heck reaction[2] (Scheme 1) due to developments which have considerably enhanced the scope of this palladium-catalysed vinylation of aryl, heteroaryl, vinyl and benzyl halides. Thus the Heck reaction has been extended to the synthesis of bridged rings, spirocycles, and tetrasubstituted carbon centres.[3-5] These latter developments and the ongoing high level of activity have been further fostered by the advent of a range of additives which variously enhance the rate of Heck reactions, control the regioselectivity of the β-hydride elimination step, and suppress double bond isomerisation in the product. Thus addition of tetraalkylammonium salts often allow Heck reactions to be carried out at, or near, room temperature in good yield,[6] whilst addition of Ag(I) salts[7] or Tl(I)[8] salts can control the direction of β-hydride elimination, suppress double bond isomerisation and influence the reaction rate. Tl(I) additives have also proved useful in natural product synthesis.[9] However, the Heck reaction fails to take advantage of the inherent ability of palladium (0) catalysts to process a wide range of chemically distinctive substrates and suffers from the drawback that, as usually practised, only one C-C bond is made.



Scheme 1

The full power of Pd(0) catalysis can be liberated by designing cascade reactions that take advantage of the diverse range of substrates accepted by these catalysts. Cascade reactions may be defined as multireaction "one-pot" sequences in which the first reaction creates the functionality to trigger the second reaction and so on .....

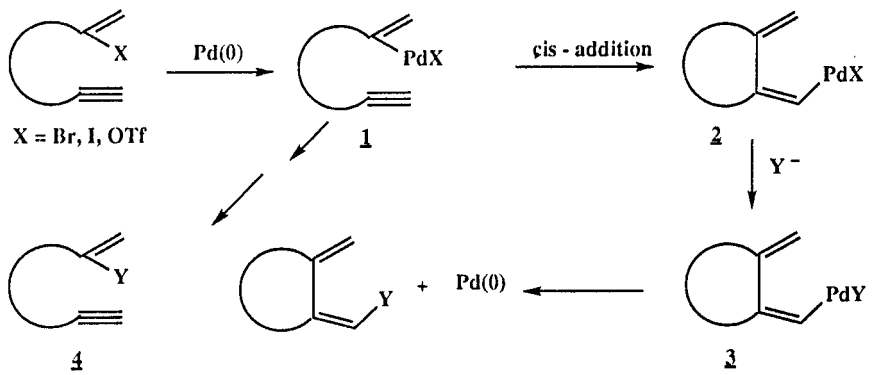
Advantages of Cascade Reactions:

1. High atom efficiency, low waste and clean technology.
2. More efficient use of manufacturing plant.
3. Major increase in molecular complexity. In industrial terms manufacturers add focused molecular complexity to simpler starting materials. Thus molecular complexity = added value.
4. The ability to assemble combinations of 2,3,4.....n different substrates involving both C-C and C-heteroatom bond formation. In this context it is useful to reflect that while enzymes are exquisitely selective catalysts they only make or break the same type of bond. On the other hand polymerisation methodology can rarely co-polymerise more than two types of monomer and control of product molecular weight and stereochemistry present substantial problems. As will be shown below Pd(0) catalysts are much more versatile and useful in assembling a wide range of substrates and bond types.
5. The ability to design cascades which switch between inter- and intra-molecular processes.

Requirements for Cascade Design.

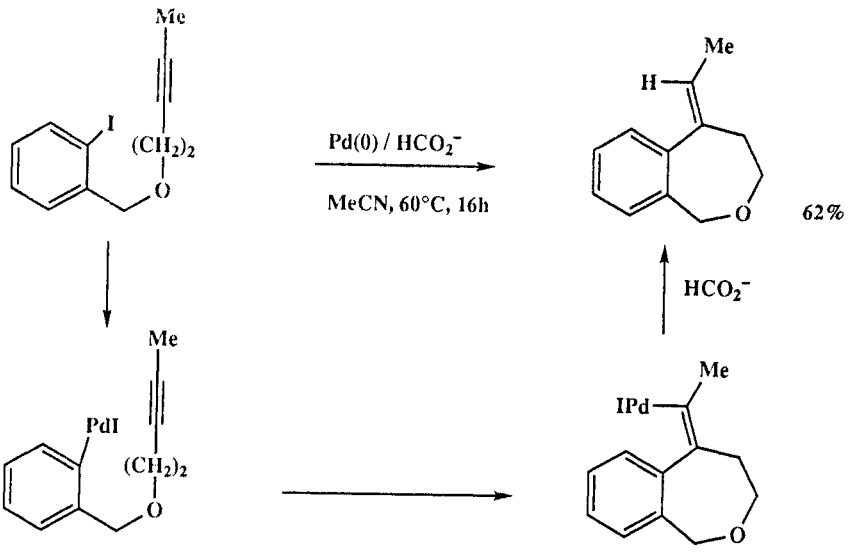
1. A good understanding of the relative rates of disparate reactions and their sensitivity to temperature and pressure.
2. An ability to engineer the control of chemo-, regio- and stereo-selectivity.
3. Mild reaction conditions.

Our initial experiments on palladium catalysed cascade reaction design focused on ring formation with concomitant incorporation of additional functionality. These studies led to our Pd(0) catalysed cyclisation-anion capture methodology outlined in Scheme 2 for a monocyclisation with an alkyne terminating (see below) species.



Scheme 2

In Scheme 2 the reaction would normally become unproductive with the accumulation of **2**. However, anion exchange of X for Y which produced **3** susceptible to reductive elimination would establish the required catalytic cycle. The deleterious direct capture or "shunt" pathway **1** → **4** would be expected to be susceptible to ring size and the nature of Y. Initial experiments with Y = hydride ion (Scheme 3)[10] established the viability of Scheme 2 for various ring sizes.



Scheme 3

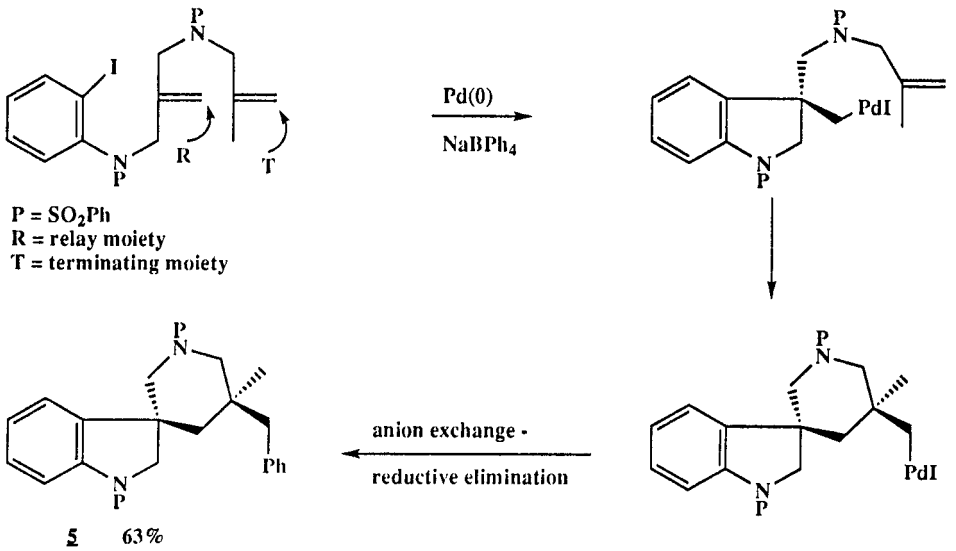
In most of the work discussed in this paper the Pd(0) catalyst was either generated *in situ* from 10 mol % $Pd(OAc)_2$/20 mol % PPh_3 or 5-10 mol % of preformed Pd(0) [$Pd[PPh_3]_4$, Pd_2dba_3] was used.

A range of sources of the hydride ion were evaluated and formate salts (HCO_2Na, HCO_2H/piperidine were found to be the most generally effective and to supress the shunt pathway. Further exploration of ring size and anion capture agent Y led to Table 1 which illustrates the scope of the cyclisation-anion capture methodology.

Table 1 Potential Combinations for (Poly) Cyclisation Anion-Capture Processes.

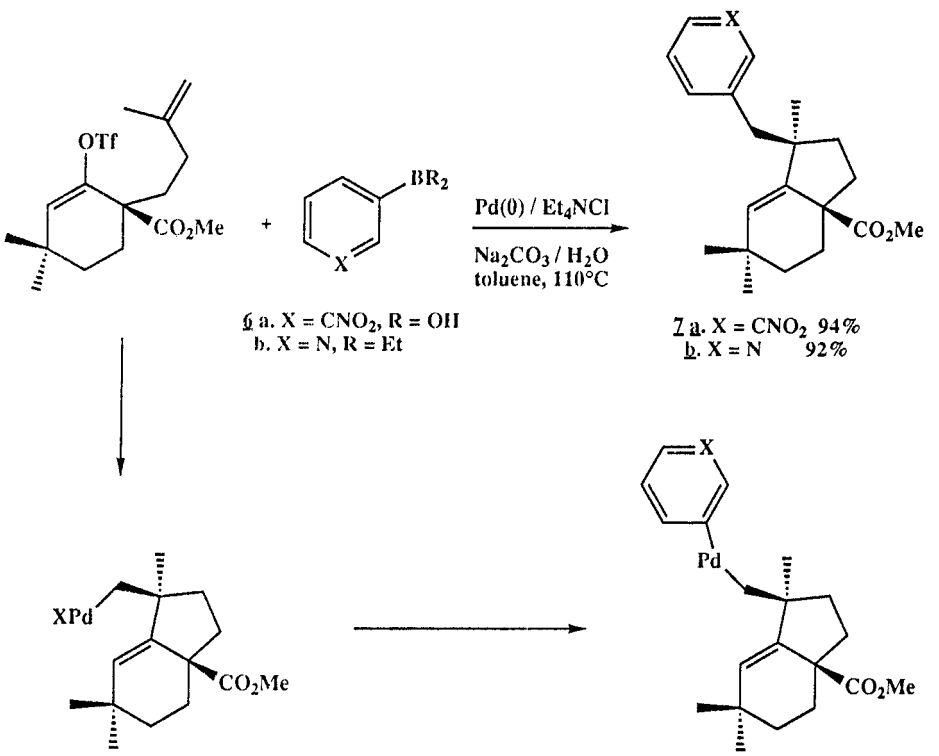
Starter Species	**Relay Species (R)**	**Terminating Species (T)**	**Y**
alkyl	alkene	alkene	**anionic** [H,OAc CN, N_3 SO_2Ph,$CH(CO_2R)_2$]
aryl	alkyne	alkyne	**neutral** (amines, MeOH/CO, acrylates)
vinyl	1,2-diene	1,2-diene	**organometallics** RM[M=Sn(1V),
allyl	1,3-diene	1,3-diene	B, Zn]
allenyl			

The Pd(0) catalyst undergoes oxidative addition to the starter species (halide, triflate, acetate etc) to generate an organopalladium(II) intermediate. In processes involving formation of one ring this intermediate successively engages the terminating species and the anion capture agent Y. In polycyclisation processes the initial organopalladium(II) intermediate engages one or more relay species before passing to the terminating phase and then anion capture. This is illustrated for a biscyclisation of an aryl starter species in Scheme 4.[11] The product **5** is obtained as a single diasteromer and the stereochemistry, which is based on a chair-like pre-transition state conformer for the second cyclisation,[12] is provisional. Note that exo-cyclisation to generate the smallest ring is invariably preferred over endo-cyclisation.



Scheme 4

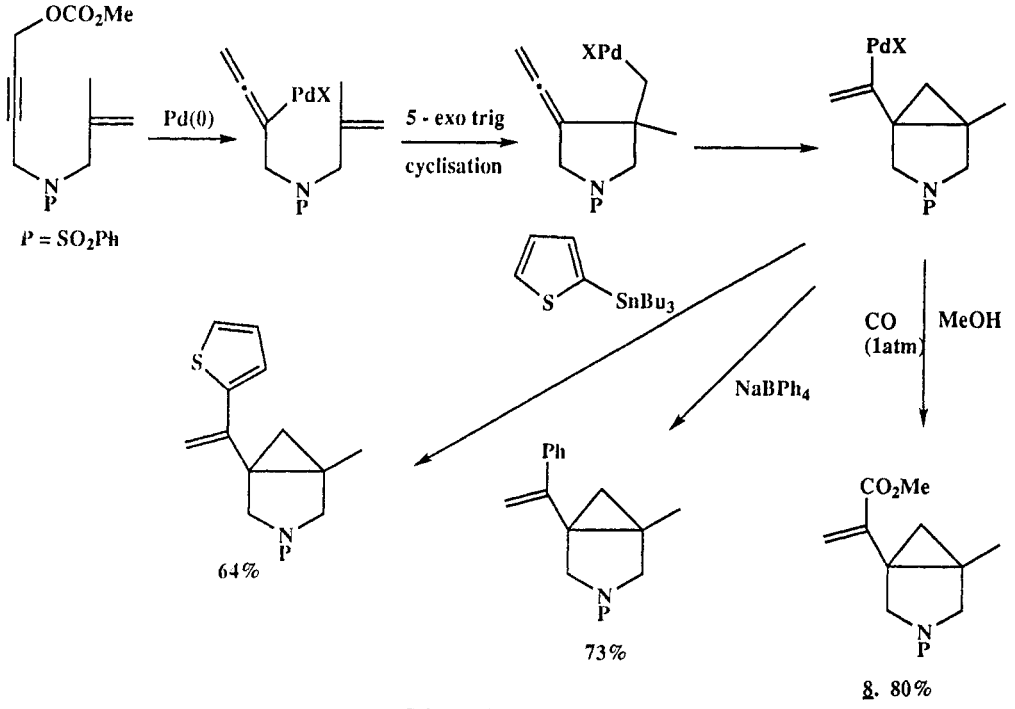
Table 1 is capable of considerable further extension especially with respect to the anion capture agent Y. Examples which employ all the starter species, terminating species and anion capture agents Y shown in Table 1 have been achieved for monocyclisation processes but not all possible combinations have been explored. With ring sizes 3 - 7 the shunt pathway is rarely a problem and additives such Et_4NCl[6] or Tl(I)[8] salt help supress this deleterious process. A typical monocyclisation process is shown in Scheme 5.[11]



Scheme 5

Oxidative addition of Pd(0) to the vinyl triflate starter species is followed by stereospecific 5-exo trig cyclisation, anion exchange with **6a** or **6b** and reductive elimination to afford **7a** and **7b** as single diastereomers in excellent yield. Boronic acids, by virtue of their ease of accessibility, stability, and diverse structures form a valuable resource for the cyclisation-anion capture methodology.

A typical biscyclisation involving formation of three new bonds is shown in Scheme 6[13] which utilises Tsuji's simple and efficient method[14] for generating allenylpalladium(II) species.



Scheme 6

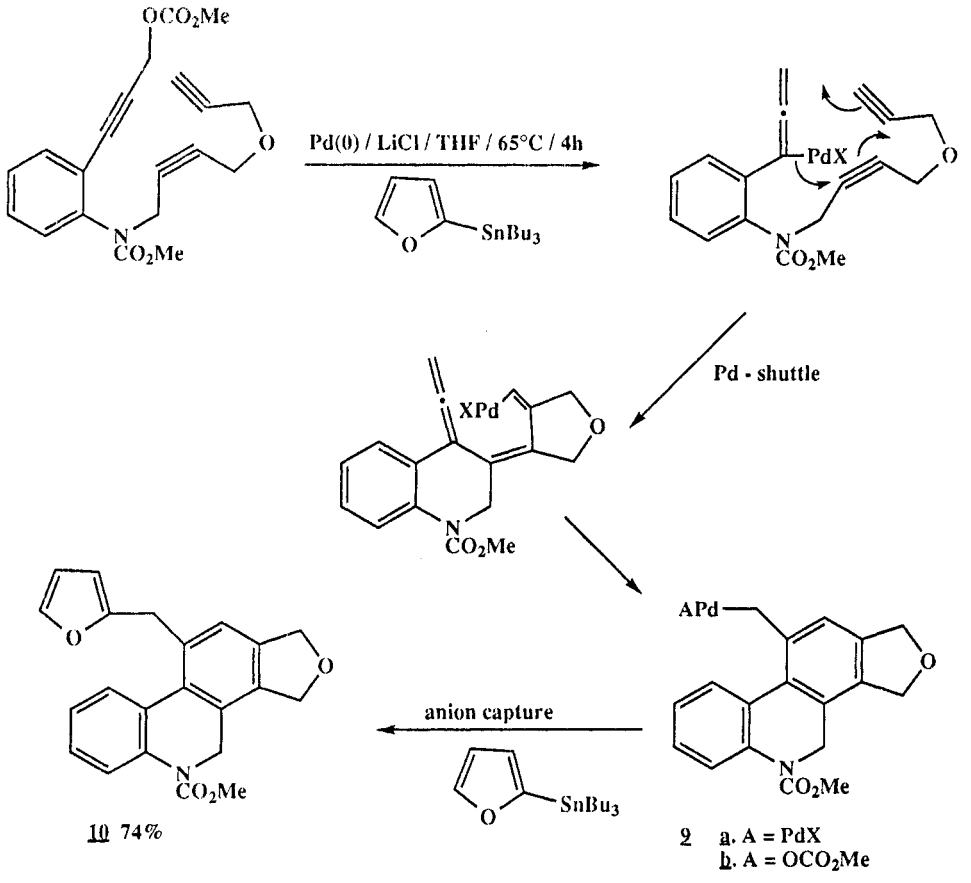
Organotin reagents $RSnBu_3$ and $RSnMe_3$ comprise a valuable source of diversity and added complexity. They are easily accessible and stable and can be readily interfaced with our relay switch reagents (see below). Tris-cyclisation-anion capture is illustrated in Scheme 7.[15]

An alternative mechanism for Scheme 7 is that involving a palladium catalysed [2+2+2]-cycloaddition to give **9b** followed by oxidative addition of Pd(0) to give **9a**, an intermediate common to both cascades. Apparently both mechanisms can operate since mixtures of **9b** and **10** are obtained under certain conditions. However, under the conditions of Scheme 7[15] **9b** is not converted into **10.**

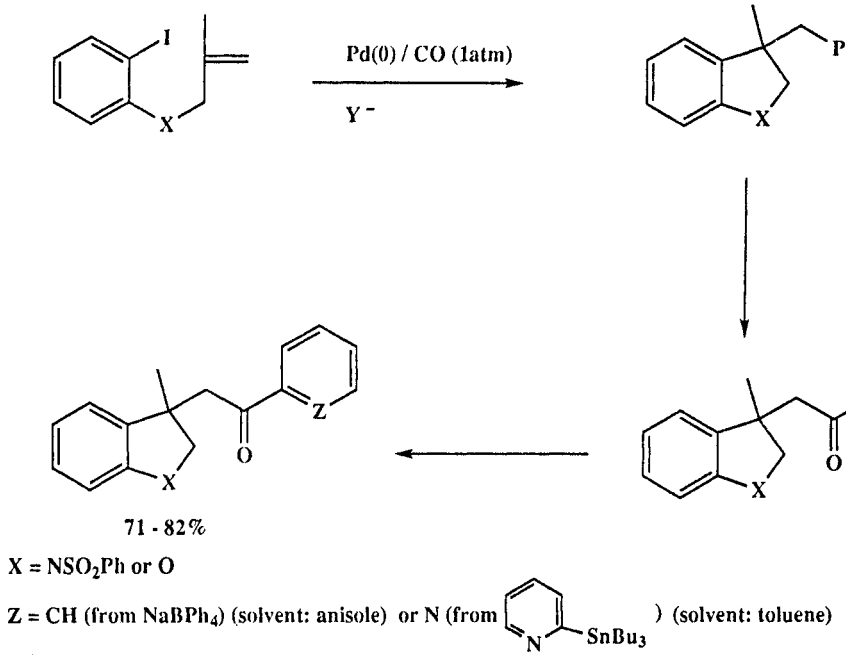
Table 1 emphasises the versatility of the general concepts but much detail remains to be explored. However, as initially conceived our cyclisation-anion capture methodology suffers from the drawback that most cascades are two component processes i.e. the ring 'zipper' precursor and Y. This shortcoming would be circumvented if polycomponent processes could be achieved by extension of the relay phase with incorporation of both inter- and intra-molecular segments. In this context the formation of the ester **8** in Scheme 6 would be an example of a 3-component process.

Initially we showed that a series of 3-component processes can be readily achieved by employing CO (1 atm) in combination with the anionic and MR groups of capture agents Y (Table 1).[16] A typical example is shown in Scheme 8.[17]

Thus the relative rates of cyclisation, carbon monoxide insertion and capture of Y allow high yielding 3-component processes to be designed where the various components can be considered to be queuing for access to the palladium centre. These polycomponent processes create the flexibility for the introduction of major increases in molecular complexity and offer rapid entry to advanced intermediates in natural

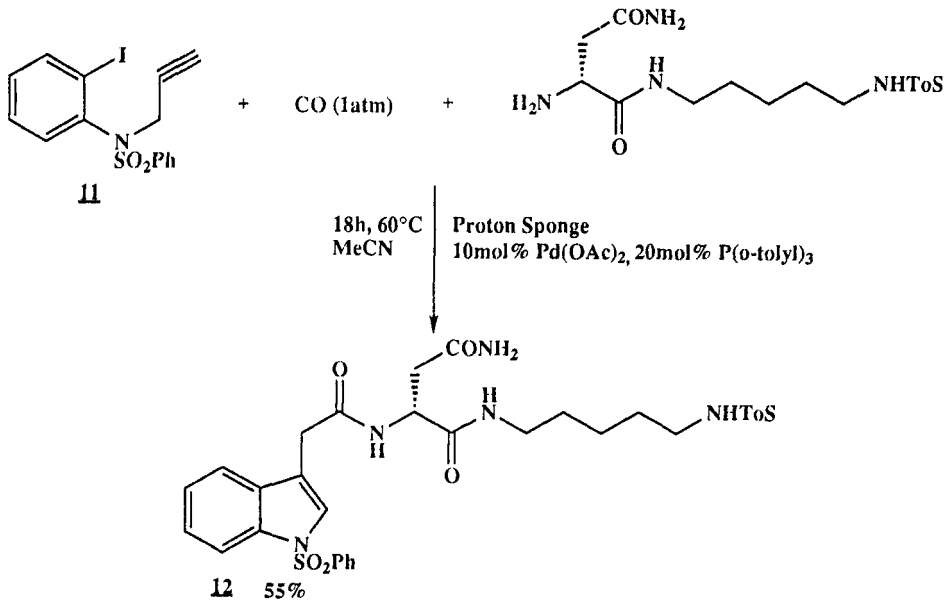


Scheme 7



Scheme 8

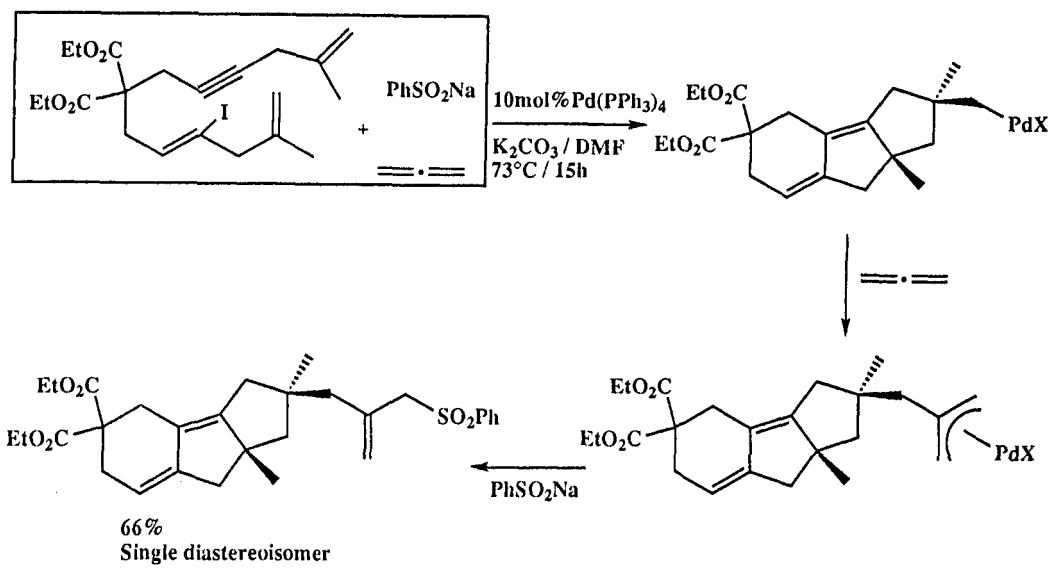
product synthesis. We have applied such 3-component processes to the synthesis of indolic spider toxins[18] of which Scheme 9, (unpublished) is an example.



Scheme 9

The precise stage at which double bond migration occurs in Scheme 9 has yet to be elucidated. Thus although the allene corresponding to **11** undergoes conversion to **12** the corresponding non-indolic exo-alkene isomer of **12** is also detected.

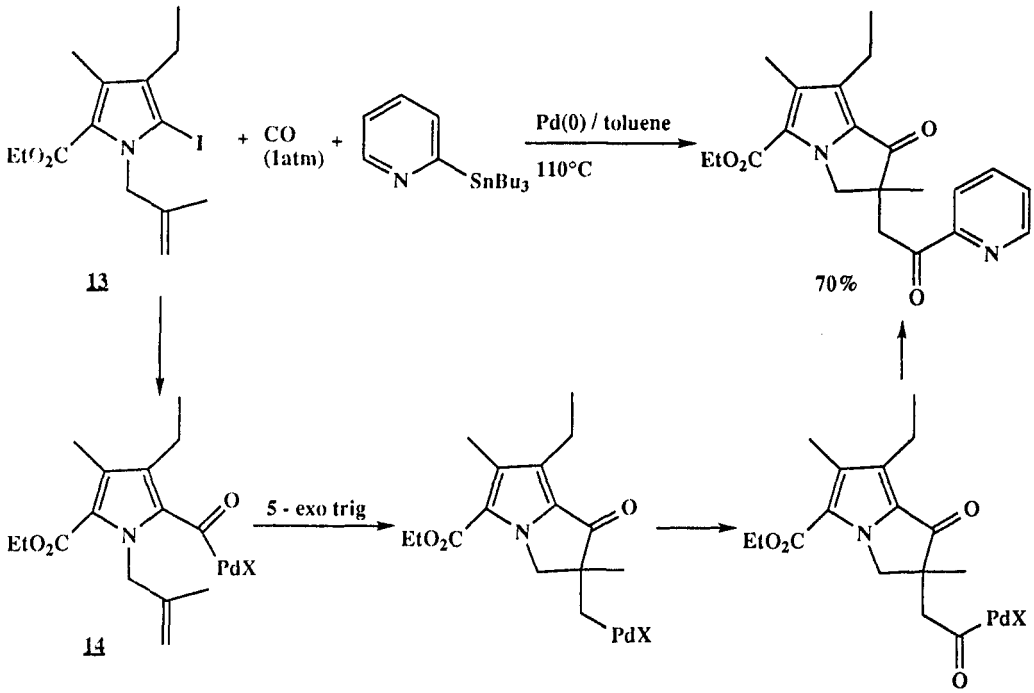
Substrates such as CO in Schemes 8 and 9 are termed relay switch reagents because they prolong the relay phase of the cyclisation-anion capture methodology whilst offering the potential to switch the cascade between intra- and inter-molecular processes. Allenes are also valuable substrates in this respect and Scheme 10 illustrates a 3-component polycyclisation cascade utilising allene (1 atm).[15]



Scheme 10

Once again a well ordered molecular queue results and the process, which involves formation of five new bonds and two stereocentres, is highly diastereoselective. The employment of allenes as relay switch components also offers great synthetic flexibility by virtue of the formation of π-allylpalladium(II) intermediates.

Tactically these polycomponent molecular queuing cascades can be engineered such that the relay switch component is incorporated pre- or post-cyclisation. A 4-component cascade (CO is utilised twice) involving the former strategy is shown in Scheme 11.[19]



Scheme 11

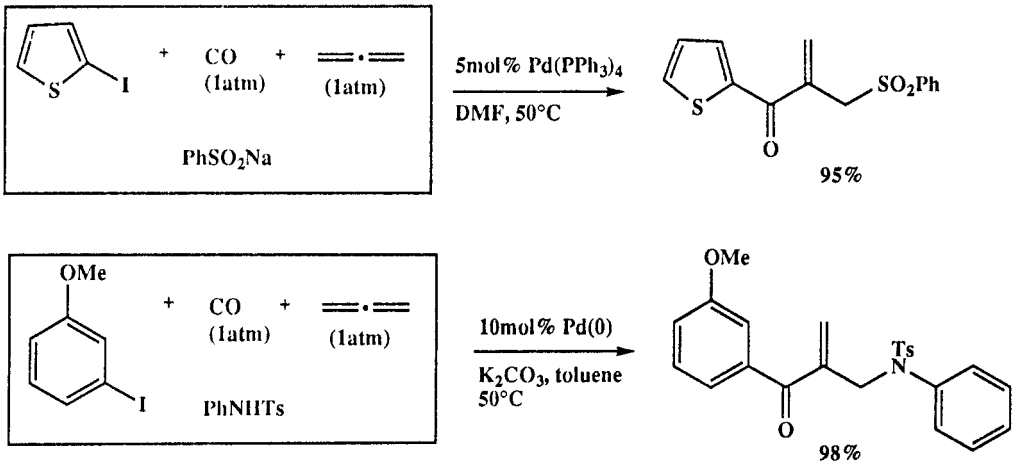
In this cascade the initial oxidative addition product from **13** and Pd(0) could conceivably undergo a 4-exo trig cyclisation. Such cyclisations are known but are expected to be slow.[11] Hence insertion of carbon monoxide occurs first to provide the acylpalladium(II) intermediate **14**. The 5-exo trig cyclisation of **14** is now fast and is followed by further incorporation of carbon monoxide with transfer of the 2-pyridyl group from Sn(IV) being kinetically the slowest process. Thus the initial relay phase step is intermolecular and is followed by an intramolecular step. In this cascade four new bonds are formed.

Examples of 4-component queuing processes employing allene and CO are shown is Scheme 12.[20] In these cascades there is an orderly molecule queue with incorporation of CO occurring prior to incorporation of allene.

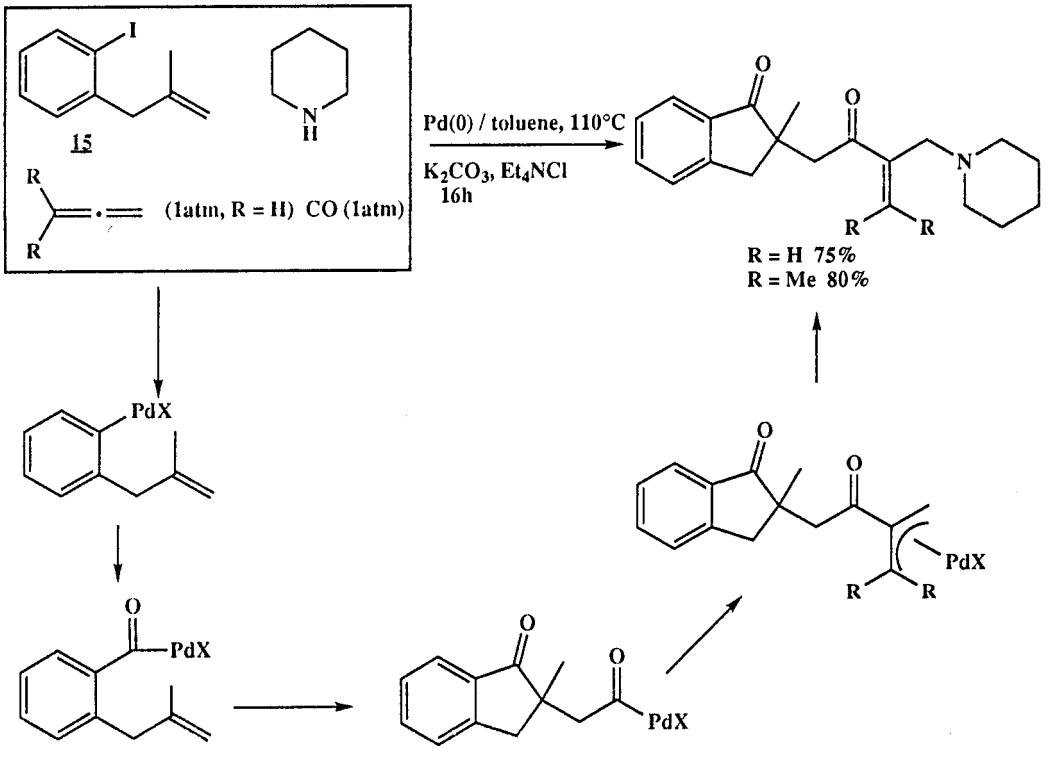
Pentamolecular queuing processes have also been achieved as illustrated by Scheme 13[21] and 14 (unpublished).

The strategy employed in Scheme 13 is analogous to that employed in Scheme 11 in that the initial oxidative addition product of **15** and Pd(0) undergoes CO insertion in preference to a 4-exo trig cyclisation. Once again orderly queuing processes occur under the reaction conditions shown and result in the formation of five new bonds with regiospecific functionalisation of the intermediate π-allylpalladium(II) species by morpholine.

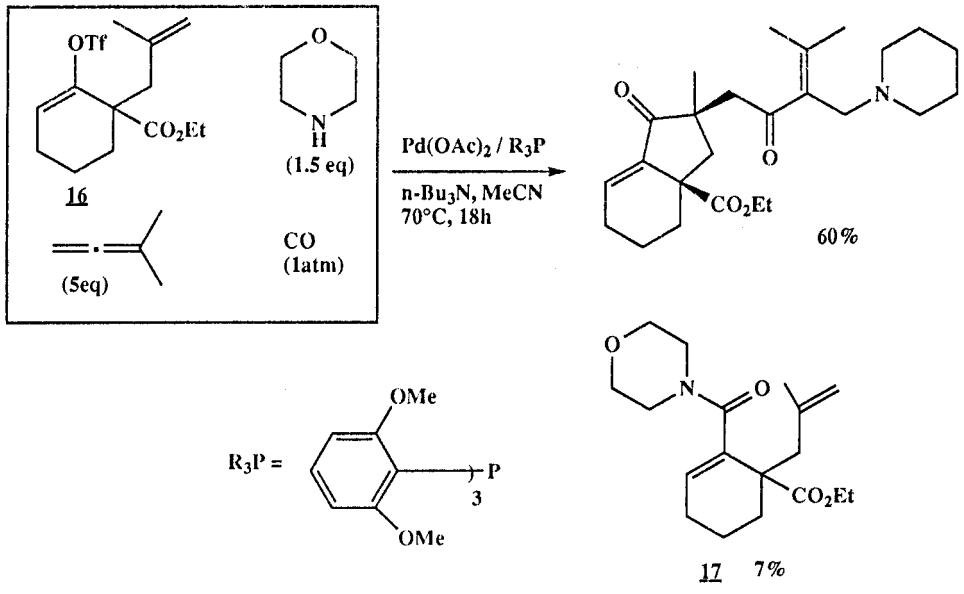
Scheme 14 illustrates an analogous process for a vinyl triflate. In this case 2,6-dimethoxyphosphine proved an effective ligand for palladium. A small amount of the direct capture product **17** was also obtained.



Scheme 12



Scheme 13



Scheme 14

In summary, our preliminary studies have shown that palladium catalysts enable the orderly assembly of diverse molecular building blocks via polymolecular queuing processes. These processes exhibit high chemo-, regio- and diastereo-selectivity and result in substantial increases in molecular complexity. The general cyclisation-anion capture methodology and relay switch reactants appear capable of substantial further development.

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